REMARKS

Status of the Claims:

Claims 1-8 and 11-36 are pending and claims 1-8 and 11-20 are under consideration in this application. Claims 17-20 have herein been amended and support for these amendments can be found, for example, on page 8, lines 23-31. No new matter has been added. Claims 9, 10, and 21-36 have been cancelled without prejudice. All of the claims under consideration stand rejected.

35 U.S.C. 112, first paragraph, rejection

Claims 17-20 stand rejected on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

From the comments at page 2, line 14, to page 4, line 3, of the Office Action, applicants understand the Examiner's position to be that, "the specification is merely speculative concerning success of an individual polypeptide as a diagnostic composition in methods for specifically detecting *M. tuberculosis* infected hosts or hosts susceptibility to *M. tuberculosis*" and thus the invention is not enabled by the specification in view of the state of the art at the time of filing.

Applicants respectfully traverse this rejection since there is ample evidence to support the contention that these polypeptides behave as claimed and defined by the specification.

The present invention is based on the discovery of a novel group of open reading frames (ORFs) encoding polypeptides that are secreted by *M. tuberculosis*, and provides for their use in diagnostic assays. As previously stated on page 13, line 18, to page 14, line 10, of the Amendment and Response of October 7, 2005, applicants submit that one of ordinary skill in the art would have expected a substantial number of the secreted *M. tuberculosis* polypeptides of the claimed methods to be useful in the diagnosis of tuberculosis. As further support for this

assertion, applicants provide a review article by A.S. Mustafa titled "Biotechnology in the Development of New Vaccines and Diagnostic Reagents Against Tuberculosis (A.S. Mustafa (2001) Current Pharm. Biotech. 2:157-173; herein referred to as Mustafa; and a copy of which is enclosed as Exhibit A). Mustafa discusses how secreted TB-antigens are highly immunogenic and were the subject of intensive investigation by artisans for this very reason. For example, on page 159, column 1, lines 26-30, Mustafa states "secreted antigens present in the culture filtrate of *M. tuberculosis* have attracted most attention because these are considered to be immunodominant and involved in protective immunity..." Moreover, a scientific article co-authored by one of the inventors of this application, Dr. Maria Laura Gennaro (Amor et al. (2005) Scandinavian J. Immunol. 61:139-146), confirmed that all five of the instantly claimed polypeptides tested were useful as diagnostics, either alone or in combination with a "prior art" polypeptide (see, for example, Amor et al., page 144, Fig. 4; and see, Office Action Response, October 7, 2005, page 13, line 23, to page 24, line 1). In Amor et al., each of the polypeptides specified by the claims (MTSP1, MTSP21, MTSP23, MTSP36, and MTSP43; or Rv0603, Rv1804c, Rv1271c, Rv2253, and Rv0203, respectively in Amor et al.), using an enzyme-linked immunosorbent assay (ELISA), were specifically recognized by antibodies in sera from a proportion of tuberculosis-infected patients. Moreover, sera from no control subjects, or from a much lower proportion of control subjects, contained such antibodies.

However, the Office action states on page 3, lines 6-12, that the Amor et al. reference was not found persuasive because: (i) "two of the claimed polypeptides MTSP1 (Rv0603) and MTSP43 (Rv0203) did not distinguish between a TB patient and a patient having lung disease other that TB...," and (ii) "[t]he remaining claimed polypeptides produced low reactivity with patient sera, i.e., at best 9/50 patients, at lowest 4/50 patients, above an arbitrary cutoff level." Applicants respectfully disagree with this position.

In response to the first point, applicants respectfully submit that the Amor et al. reference does show the two proteins of the claimed methods, Rv0603 and Rv0203, are antigenic/immunogenic and useful in TB serodiagnosis in patients. The authors' comments that "two of the claimed polypeptides MTSP1 (Rv0603) and MTSP43 (Rv0203) did not distinguish between a TB patient and a patient having lung disease other that TB" were in view of the raw data presented in Figure 3, which shows serological reactivity of the five novel secreted proteins

(of the instantly claimed methods) by comparison of patient (e.g., TB-positive subjects) and control populations. However, this in no way indicated that the two proteins lacked diagnostic potential or value. Quite the contrary, these proteins were believed to have and shown to have diagnostic utility as called-out first in the Abstract of Amor et al., page 139, lines 15-17, "thus at least five novel secreted proteins [Rv0203, Rv0603, Rv1271c, Rv1804c, and Rv2253] induce antibody responses during active disease," and demonstrated by the data presented in Figure 4 (see Amor et al., page 144).

Figure 4 of Amor et al. presents a re-analysis of the raw data of Figure 3 in which a cutoff value was set (i.e., + 3 standard deviations of ELISA readings from 48 non-TB control sera) – those patient test results which fell above the cutoff were determined to be "TB-positive" and those patient test results which fell below the cutoff were designated "TB-negative." Under these criteria, 8% (for Rv0203) and ~12% (for Rv0603) of TB-positive patients were sero-reactive to these two antigens, indicating that the two antigens are indeed useful in diagnostic tests for TB. Notably, using these criteria, the two polypeptides were not recognized by sera from any non-TB infected patients (control sera). Furthermore, one of the proteins, Rv0203, in combination with Rv1271 (MTSP23) further enhanced the predictive power of the p38 antigen (capturing 68% of TB-positive patients) in determining whether or not a patient was TB-positive (see, Figure 4, page 144, one column set from extreme right, and page 145, column 1, lines 10-11). Applicants respectfully point out that the analysis presented in Figure 4 of Amor et al is typical of how data from diagnostic tests are processed and provides more reliable diagnostic information than the raw data analysis presented in Figure 3.

In response to the second point raised by the Office Action, applicants respectfully submit that there is no requirement that the polypeptides used in the claimed methods perform better or even equivalently to those in the prior art. The only requirement is that the polypeptides of the claimed methods function as claimed and defined by the specification (see, for example, *Raytheon Co. v. Roper Corp. 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984).* "An invention need not be the best or the only way to accomplish a certain result, and it need only be useful to some extent and in certain applications...[;]" *Cf. Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc., 807 F.2d 955, 960 n.12, 1 USPQ2d 1196, 1199 n.12 (Fed. Cir. 1986`).* "It is possible for an invention to be less effective than

existing devices but nevertheless meet the statutory criteria for patentability[;]" or *E.I. du Pont De Nemours and Co. v. Berkley and Co., 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980).* "The claimed invention must only be capable of performing some beneficial function... An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely....").

At page 3, lines 13-17, of the Office Action, the Examiner objects to the cited Amor et al. reference stating that "the method being claimed is not the method in the cited reference [Amor et al.]." Applicants respectfully point to M.P.E.P. 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic'....A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." Indeed applicants respectfully submit that one skilled in the art would have believed that subjects whose sera showed reactivity in the ELISA assay of Amor et al. would very likely also have shown positive responses in the assay of claim 17, e.g., a skin test assay.

The Office Action also alleges at page 3, lines 19-20, that the "Amor et al. [reference] does not teach that the polypeptides can be utilized to diagnose a subject who is 'susceptible' to *M. tuberculosis*, as is claimed in the instant invention." While applicants respectively disagree with this position, to expedite the prosecution of this application, this term has been deleted from the first and second method steps of claims 17-20. In light of these amendments, applicants respectfully submit that this objection is moot.

From the comments on page 3, lines 17-18, of the Office Action, applicants understand Examiner's position to be that "functional segments" of a TB-specific polypeptides are not enabled by the specification. Applicants respectfully disagree with this position.

A functional segment of a TB-specific polypeptide, as defined in the specification, is "a segment of the polypeptide that has *Mycobacterium tuberculosis* specific antigenic and immunogenic properties." A polypeptide that has these properties, as defined by the specification (see page 7, line 18 to page 8, line 3), only need be recognized by and bind to antibodies elicited in response to *Mycobacterium tuberculosis* organisms or wild-type *Mycobacterium tuberculosis* molecules (e.g., polypeptides) and be able to elicit the production of antibodies that recognize and bind to Mycobacterium tuberculosis organisms or wild-type Mycobacterium tuberculosis

molecules (e.g., polypeptides). In view of: (a) this definition, or an even more rigorous definition in which the relevant antibodies bind to, for example, mycobacteria only of the *Mycobacterium tuberculosis* Complex; (b) the routine nature of testing for these antigenic and immunogenic properties; and (c) the small size of the these polypeptides, applicants submit that one of ordinary skill in the art would readily be able to identify segments of these polypeptides having the requisite function (although not necessarily the same level of function as corresponding full-length MSTP polypeptides). Moreover, doing so would not constitute undue experimentation.

In view of these considerations and amendments, applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

35 U.S.C. § 112, second paragraph, rejection

Claims 1-8 and 11-20 stand rejected as allegedly indefinite for failing to point out and distinctly claim the subject matter that the applicant regards as the invention. Applicants respectfully traverse this rejection.

At page 4, lines 18-20, the Office Action states "the specification does not provide guidance to which sequences and resulting polypeptides have the claimed M. tuberculosis specific antigenic and immunogenic properties."

As discussed above, a polypeptide having *Mycobacterium tuberculosis*-specific antigenic and immunogenic properties, as defined by the specification (see specification, page 7, lines 18-22; and page 7, line 30 to page 8, line 3), is one that can be recognized by and bind to antibodies elicited in response to Mycobacterium tuberculosis organisms or wild-type Mycobacterium tuberculosis molecules (e.g., polypeptides), and can elicit the production of antibodies that recognize and bind to Mycobacterium tuberculosis organisms or wild-type Mycobacterium tuberculosis molecules (e.g., polypeptides). This definition does not require that the relevant molecules elicit immune responses to molecules only expressed by the *Mycobacterium tuberculosis* Complex. In view of this definition, and especially in light of the teaching of the Mustafa et al. reference (see above), applicants respectfully submit that those skilled in the art would expect that most, if not all, of specified polypeptides would have *Mycobacterium tuberculosis*-specific antigenic and immunogenic properties.

Despite these considerations, and as shown by Table 2 of Amor et al. (page 142), all of the polypeptides specified by the instant claims are in fact specifically expressed by bacteria of the *Mycobacterium tuberculosis* Complex. The relevant polypeptides are MTSP15, 21, 25, 36, 43, and 47 (designated Rv0617, Rv1804c, Rv2398c, Rv2253, Rv0203, and Rv2290, respectively, in Amor et al.). In view of these findings, it is very likely that antibodies elicited by these polypeptides would not detect infections by mycobacteria other than those of the *Mycobacterium tuberculosis* Complex

In light of the above factors, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In summary, for the reasons set forth above, applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action and permit the claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension of time. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07763-042001.

Respectfully submitted,

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